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Gene Section
Short Communication

USB1 (U6 snRNA biogenesis 1)

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Abstract

C16orf57 alias USB1 is the gene which mutations underlie poikiloderma with neutropenia (PN) syndrome, a rare genodermatosis with autosomic recessive inheritance.
PN patients have an increased risk to develop myelodysplasia and acute myeloid leukaemia in the second decade of life.
In 2012, the protein encoded by USB1 has been recognised to be a 2H phosphodiesterase involved in the processing of U6 snRNA, but its action pathway and hence role in the pathogenesis of PN has not yet been elucidated.

Identity

Other names: C16orf57, EC 3.1.4., hUsb1, HVSL1, Mpn1, PN

HGNC (Hugo): USB1

Location: 16q21

DNA/RNA

Description

According to UCSC database (GRCh37/hg19, Feb.2009), USB1 gene maps in the region between 58035277 and 58055527 bp from pter of chromosome 16 with a centromeric-telomeric orientation.
It spans 20 kb and is composed of seven exons (GI:305855061; NM_024598.3) (Fig.2).

Transcription

Two physiological isoforms, generated by alternative splicing (Fig. 2), have been detected in normal samples (leucocytes, keratinocytes, melanocytes and fibroblasts). The major transcript of 2282 nt (isoform 1, NM_024598.3) includes all the seven exons of the gene, while the shorter isoform of 1217 nt (NM_001204911.1) comprises the first three exons and an alternative terminal fourth exon located in IVS3 (Arnold et al., 2010).

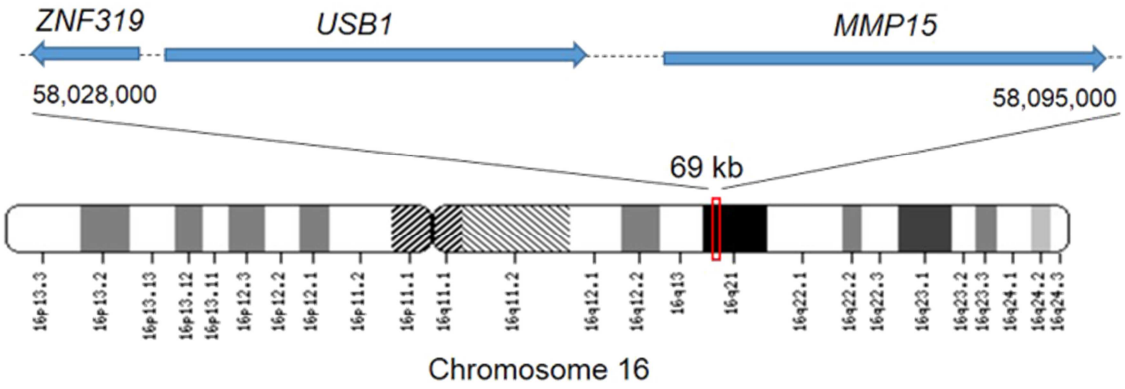


Figure 1. The region on chromosome 16q21 containing USB1 and its neighbouring genes ZNF139 (zinc finger protein 319) and MMP15 (matrix metalloproteinase 15) (UCSC database -GRCh37/hg19, Feb 2009).

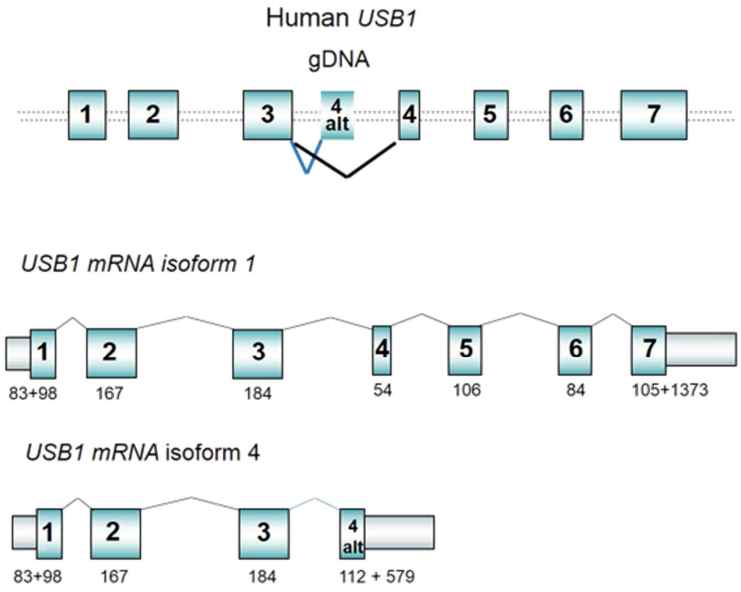


Figure 2. Schematic representation of exon-intron structure of USB1 and the two major transcripts resulting from alternative splicing of the two mutually exclusive exons 4.

Several additional transcripts, a few detected in cancer samples, are reported in the Ensembl database.

Pseudogene

No pseudogene for USB1 is known.

Protein

Description

The crystal structure of the human USB1 protein, translated by isoform 1 mRNA has been recently resolved (Hilcenko et al., 2013).

The main USB1 protein comprises 265 aa, while translation of isoform 4 mRNA predicts a 186 amino acid protein with a different C-terminus.

The USB1 protein is characterized by two tetrapeptide motifs (HLSL), containing histidine and serine residues (H120, S122, and H208, S210) which are essential for its catalytic activity. Recognition of these motifs by computational analysis of the protein sequence has predicted USB1 belongs to the 2H phosphodiesterase superfamily present in bacteria, archea and eukaryotes (Colombo et al., 2012).

The protein has a globular architecture with two juxtaposed lobes with a pseudo two-fold symmetry separated by a central groove, which exposes the two HLSL motifs of the active site (Fig.3).

Expression

USB1 is ubiquitously expressed in humans (Volpi et al., 2010).

The high evolutionary conservation of the protein is consistent with the housekeeping function of the gene.

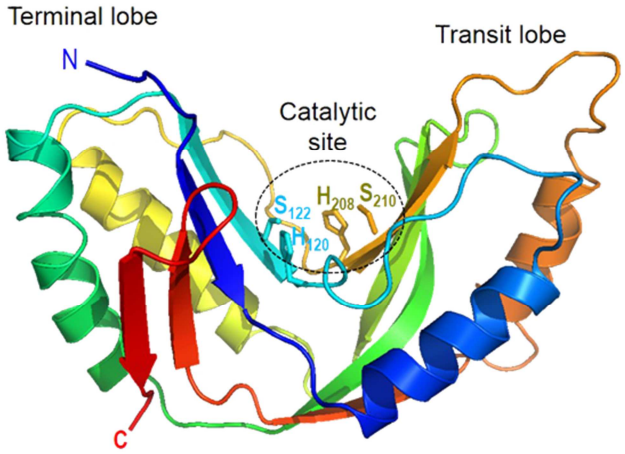


Figure 3. Ribbon model of the USB1 protein showing its globular symmetrical conformation with two lobes separated by a central groove that exposes the catalytic site containing the two HLSL motifs (encircled). The terminal lobe comprises both the N- and the C-termini. Both the terminal and transit lobe consist of antiparallel β-sheets and α-helices (modified from Colombo et al., 2012).

Localisation

A nuclear localization of USB1 has been demonstrated in HeLa cells (Mroczek et al., 2012); both nuclear and mitochondrial localizations have been observed for the yeast orthologue (Glatigny et al., 2011).

Function

Usb1 is a 3'-5' RNA exoribonuclease that trims the 3' end of the U6 snRNA leading to the formation of a terminal 2',3' cyclic phosphate. This post-transcriptionally modification influences U6 stability and recycling. Evidence has been obtained in yeast where Usb1 depletion leads to reduced levels of U6, generalized pre-mRNA splicing defects and shorter telomeres. In human use of PN cell lines confirmed that U6 is a substrate of USB1, but failed to reveal a splicing defect leaving unsolved how PN develops (Hilcenko et al., 2012; Mroczek et al., 2012; Shchepachev et al., 2012).

Mutations

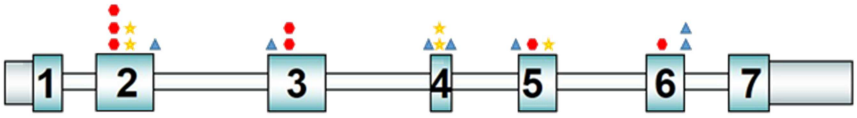
Germinal

Biallelic mutations in USB1 gene (OMIM*613276) cause poikiloderma with neutropenia syndrome (OMIM#604173).

To date, 19 different "loss-of-function" mutations have been identified in 38 molecularly tested PN patients: 7 non-sense mutations, 6 out-of-frame deletions and 6 canonical splice site mutations. The latter also include the only missense mutation so far reported which however leads to exon skipping (Volpi et al., 2010). Recurrent mutations can be identified in patients of Navajo, Turkish and Caucasian origin attesting a founder effect (Colombo et al., 2012).

Somatic

No information is currently available on mutations of USB1 in sporadic cancers.



USB1 position	Symbol	Mutation	Protein effect
Ex 2	★	c.176_177delGG	p.(Gly59Alafs*2)
	★	c.179delC	p.Pro60Leufs*55
	●	c.232C>T	p.Arg78*
	●	c.243G>A	p.(Trp81*)
	●	c.258T>A	p.(Tyr86*)
IVS2	▲	c.265+2T>G	p.Tyr89Trpfs*3
	▲	c.266-1G>A	?
Ex 3	●	c.267T>A	p.(Tyr89*)
	●	c.415C>T	p.(Gln139*)
IVS3	▲	c.450-2A>G	?
Ex 4	★	c.489_492del4	p.(Asn163Lysfs*101)
	★	c.499delA (c.496delA)	p.(Thr167Profs*98)
	▲	c.502A>G	p.Phe151_Arg168del
IVS4	▲	c.504-2A>C	p.Thr169Ilefs*61
Ex 5	★	c.531delA	p.His179Metfs*86
	●	c.541C>T	p.(Gln181*)
Ex 6	●	c.673C>T	p.(Gln225*)
	▲	c.683_693+1del12	p.D204_Q231del
IVS6	▲	c.693+1G>T	p.D204_Q231del

Figure 4. Map across the USB1 gene of the currently known 19 mutations. Nonsense mutations are represented with a red hexagon, deletions with a yellow star and splicing mutations with a blue triangle. The Table lists for each mutation the intragenic position, the description (cDNA nomenclature) and the effect at the protein level.

Implicated in

Poikiloderma with neutropenia syndrome (PN)

Note

The disease is caused by mutations affecting the gene represented in this entry.

The clinical presentation of PN patients partially overlaps that of patients affected with Rothmund-Thomson syndrome (RTS; OMIM#268400) and dyskeratosis congenita (DC; OMIM#613987, #613988, #613989, #615190, #224230).

Disease

Poikiloderma with neutropenia is a rare inherited genodermatosis characterized by skin alterations (poikiloderma, nail dystrophy, palmo-plantar hyperkeratosis), short stature and non cyclic neutropenia.

In infancy, neutropenia is responsible of the recurrent infections, mainly of the respiratory system, observed in PN patients and, later in life, may lead to myelodysplastic syndrome and acute myeloid leukaemia. Squamous cell carcinoma has also been reported in PN patients.

To date, 38 out of 66 PN patients described in literature have been molecularly tested and found to carry biallelic mutations of the USB1 gene. Most of the reported patients carry homozygous mutations, attesting inheritance by descent of the same ancestral mutation.

Prognosis

The knowledge of USB1 3D structure with the essential amino acid motifs of the catalytic site might enhance the prediction of USB1 mutation effects.

All the mutations reported so far in PN patients (no. 19) interfere with USB1 function: 16 disrupt the catalytic activity due to the loss of one or both HLSL motifs, while the remaining 3 mutations, although not affecting the catalytically active tetrapeptide motifs destroy the internal symmetry of the protein. Owing to the restricted number of molecularly characterised PN patients no mutation-phenotype correlations have emerged suitable to stratify the patients according to life-long cancer risk (myelodysplasia and solid tumours).

Further studies focussing on the alternative transcript are necessary to establish the role of isoform 4 on PN pathogenesis and prognosis.

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